The Risk of Congenital Malformations Associated With Exposure to β-Blockers Early in Pregnancy
A Meta-Analysis

Mohammad Y. Yakoob, Brian T. Bateman, Eugenia Ho, Sonia Hernandez-Diaz, Jessica M. Franklin, Julie E. Goodman, Rebecca A. Hoban

Abstract—β-blockers are commonly used during the first trimester of pregnancy. Data about risks of congenital anomalies in offspring have not been summarized. We performed a meta-analysis to determine teratogenicity of β-blockers in early pregnancy. A systematic literature search was performed using PubMed, EMBASE, Cochrane Clinical Trials, and hand search. Meta-analyses were performed using random-effects models based on odds ratios (ORs). Prespecified subgroup analyses were performed to explore heterogeneity. Randomized controlled trials or observational studies examining risks of congenital malformations associated with first trimester β-blocker exposure compared with no exposure were included. Thirteen population-based case–control or cohort studies were identified. Based on meta-analyses, first-trimester oral β-blocker use showed no increased odds of all or major congenital anomalies (OR=1.00; 95% confidence interval, 0.91–1.10; 5 studies). However, in analyses examining organ-specific malformations, increased odds of cardiovascular defects (OR=2.01; 95% confidence interval, 1.18–3.42; 4 studies), cleft lip/palate (OR=3.11; 95% confidence interval, 1.79–5.43; 2 studies), and neural tube defects (OR=3.56; 95% confidence interval, 1.19–10.67; 2 studies) were observed. The effects on severe hypospadias were nonsignificant (1 study). Causality is difficult to interpret given the small number of heterogeneous studies and possibility of biases. Given the frequency of this exposure in pregnancy, further research is needed. (Hypertension. 2013;62:375-381.) ● Online Data Supplement

Key Words: β-blockers □ cleft lip/palate □ congenital anomalies □ heart defects, congenital □ neural tube defects □ pregnancy □ trimester, first

There has been a rapid rise in the use of antihypertensive medications in pregnancy during the past decade. Recent data demonstrate that the most common first-trimester antihypertensive exposure is β-adrenergic blocking agents, with nearly 0.5% of all pregnant women exposed to these medications during this trimester. The most concerning potential adverse effect of first-trimester medication exposure is teratogenicity. Each year, ≈3% of infants are born with serious birth defects; malformations are the leading cause of infant mortality in the United States. Most β-blockers are designated by the US Food and Drug Administration as class C, meaning that animal studies have demonstrated adverse fetal effects but there are no adequate or well-controlled studies in humans.

Despite the frequency of this exposure, data about risks of fetal congenital anomalies associated with first-trimester use of oral β-blockers have not previously been summarized. Therefore, we undertook this systematic review and meta-analysis to combine data from existing randomized controlled trials, cohort, and case–control studies to answer the hypothesis that first-trimester β-blocker exposure may be associated with birth defects.

Methods

Search Strategy

The search engines used included PubMed (1966 to August 2011), EMBASE (1982 to August 2011), Cochrane Clinical Trials, controlled-trials.com, and clinicaltrials.gov to identify all published studies on β-blocker use and congenital anomalies in all languages. References of selected articles were also hand searched to ensure all possible articles were captured.

Combinations of MeSH and text words in our search string in PubMed and EMBASE included the following: antihypertensive agent/therapy; β-adrenergic receptor blocking agent/β-blocker/β-antagonist/adrenergic β-3 receptor antagonists/adrenergic β-2 receptor antagonists/adrenergic β-1 receptor antagonists, antiadrenergic, antianxiety agents, generic names of all β blockers AND pregnancy/pregnant woman/pregnancy* AND congenital disorder/congenital abnormality/congenital anomaly/congenital malformation or birth defects/defor-mit*. The Cochrane Library, clinicaltrials.gov, and controlled-trials.
Inclusion/Exclusion criteria
All available randomized controlled trials, cohort, and case–control studies were selected. The inclusion criteria were exposure of pregnant women to ≥1 oral β-adrenergic receptor blocking agents during the first trimester of pregnancy versus no use of these drugs in this time frame, and an outcome measure of ≥1 congenital anomalies. We excluded studies that were cross-sectional, descriptive, or case series/reports. Studies examining treatment of hypertensive disorders of late pregnancy, including gestational hypertension and preeclampsia/eclampsia, were excluded because late pregnancy exposures are beyond the pathologically relevant gestational period. We also excluded studies in which subjects used β-blockers to treat thyroid disorders because these disorders may be independently associated with congenital anomalies.

Selection and Quality Assessment
The titles and abstracts were reviewed independently by 2 reviewers (R.A.H. and M.Y.Y.), who then retrieved all potential full-text articles based on abstracts. Non-English articles meeting eligibility criteria were translated into English using software available online. Authors were contacted for clarification in circumstances where data were not clear or were difficult to interpret (see Results section). The reviewers (R.A.H. and M.Y.Y.) also independently assessed study quality based on criteria determined by all authors. The most important 2 factors that were thought to potentially influence study validity and quality were the following: (1) whether the study excluded or adjusted for preexisting diabetes mellitus (as diabetes mellitus may be associated with β-blocker use and is independently associated with congenital anomalies); and (2) potential for recall bias (in which women with affected babies could be more likely to recall exposure to drugs). Possible recall bias was assessed based on whether data collection involved retrospective maternal interviews or self-report of β-blocker exposure after the outcome had occurred compared with data collection that was prospective or relied on preexisting prenatal medication records (where recall bias would be unlikely).

Data Extraction
Two authors (R.A.H. and M.Y.Y.) independently extracted data from original full-text articles using a standardized data collection form. Data extracted included study type, data source, study location, primary indication for β-blocker use, timing of exposure, class(es) of malformation(s), confounders adjusted for, sample size, odds ratios (ORs; adjusted if available) and 95% confidence intervals (CIs), study exclusion/adjustment for diabetes mellitus, and potential for recall bias. Extracted data were compared and discrepancies resolved by discussion among all authors. Where multiple articles existed from a single database, the ones covering unique time periods or the most complete data were used. Data from studies having multiple data sets using the same control group were adjusted for potential multiple comparison issue1 by performing sensitivity analyses to confirm the robustness of results.

Statistical Analysis
The primary outcomes analyzed were all congenital anomalies. Various organ-specific anomalies were also studied, including cardiovascular (CV) defects, cleft lip/palate (CL/P), neural tube (NT) defects, and severe hypospadias. These organ-specific outcomes were decided post hoc based on available data. OR was the priori metamer of choice given expectations that most studies would be case–control in design. When stated/available in the articles, adjusted ORs were used. If adjusted ORs were not available, raw numbers were used to compute ORs with 95% CIs. The included studies were meta-analyzed (separately for studies that analyzed all or major malformations overall and studies that specified organ system-specific anomalies, as appropriate). The specific β-blocker medication varied or was often not stated. DerSimonian-Laird random effects was the a priori model of choice given our assumption of high heterogeneity. Heterogeneity among studies was determined using visual inspection of forest plots and I² statistic. An I² value of >30% was taken to indicate substantial heterogeneity.

Prespecified subgroup analyses were performed for outcomes where substantial heterogeneity was found. This was based on the main quality criterion of study adjustment or exclusion of diabetics. The studies were also stratified according to potential for recall bias and indication of β-blocker use. Publication bias was analyzed by visual inspection of funnel plots and the Egger test. A 2-tailed P value of <0.05 was considered to indicate publication bias. If such bias was found, a trim-and-fill plot was used to address potential missing studies and to obtain pooled estimates after adjusting for this bias.

We used 3 data sets from Puhó et al for the CL/P analysis (all with the same control group) and 2 data sets from Medveczky et al for the NT defects analysis (both with the same control group). Therefore, we performed sensitivity analyses, removing 2 studies at a time for the CL/P analysis and 1 study at a time for the NT defects analysis to assess overall robustness of the results after accounting for this multiple comparison issue.

Power calculations were performed post hoc after all studies had been collected using methodology described by Caiři et al.10 The power was 96.0% to detect an OR of 1.20 for all or major anomalies, 72.1% for an OR of 2.00 for CV defects, 97.9% for an OR of 3.10 for CL/P, and 60.9% for an OR of 3.50 for NT defects. For details about the macro and SAS code used, refer to the online-only Data Supplement. Meta-analyses were performed in Review Manager Version 5.0 (RevMan Version 5.0, Cochrane Collaboration, 2008).

Results
Electronic searches identified 2582 citations; 2462 citations remained after duplicates were removed. After title and abstract screening, 101 abstracts were selected for full-text review and 13 (9 case–control10,11–19 and 4 cohort)20–23 studies met the inclusion criteria. We did not identify any published randomized controlled trials. The search flow diagram is given in Figure 1. Details of included studies, including quality grading, are given in the Table. Sipek et al19 written in Czech, was translated into English, but was excluded because the author did not respond to queries about numbers and interpretation of study results. Furthermore, the Zagreb-based part of Erić et al22 was excluded because timing of β-blocker exposure could not be determined. The exposure comparison in all remaining included studies was use of oral β-blockers versus none. All studies were performed in developed countries: 3 in the United States,12,15,20 3 in Hungary,8,9,11 3 in Sweden,14,21,23 and 1 each in Canada,15–17 Germany,18 and Serbia.22 The timing of exposure was first trimester in all studies. In the Puhó et al study, however, a portion of the data (on posterior cleft palate) reported use in the third and fourth months of pregnancy, just past the first trimester. This study used a slightly later definition of the window of teratogenicity attributable to embryological timing of palatal fusion (and, therefore, cleft palate), and so was included. The indication for β-blockers was hypertension alone in 6 studies,4,12,13,15,17,22 hypertension and other diseases in 2 studies,1,12 and unspecified/not given in the remaining 4 studies10,14,18,22 (Table).

Details of data used for the meta-analyses are given in Table S1 in the online-only Data Supplement. Based on the meta-analysis of the 5 studies that analyzed all or major malformations (not organ specific), use of β-blockers during the first trimester of pregnancy was not associated with increased odds in the random-effects model (OR=1.00; 95% CI, 0.91–1.10; Figure 2). There was no evidence of heterogeneity (F=0%)
Figure 1. Flow diagram of literature search. RCTs indicate randomized controlled trials.

or publication bias (Egger $P=0.27$). None of these studies adjusted or excluded for diabetes mellitus (adjustment status of 1 study$^{11}$ was not clear), so subgroup analysis with this quality factor could not be performed. Studies with potential for recall bias showed similar results (OR=1.01; 95% CI, 0.91–1.13) to studies that did not have this possibility (OR=0.96; 95% CI, 0.79–1.18; Figure S1). Studies using hypertension only as indication for $\beta$-blocker use showed similar results (OR=0.97; 95% CI, 0.79–1.19) to studies where indication was hypertension and other cardiovascular disorders (OR=1.01; 95% CI, 0.91–1.13) and where indication was unspecified (OR=0.90; 95% CI, 0.29–2.75; Figure S2).

Studies that detailed organ-specific malformations were each meta-analyzed by organ system. In these post hoc secondary analyses, there was a statistically significant increase in odds of CV abnormalities (OR=2.01; 95% CI, 1.18–3.42; 4 studies). There was evidence of substantial heterogeneity ($I^2=52\%$), but no evidence of publication bias (Egger $P=0.13$). Subgroup analyses of studies that excluded/adjusted for diabetes mellitus remained significant (OR=2.72; 95% CI, 1.90–3.90; Figure 3A), and this quality factor accounted to some extent for heterogeneity. However, there was no association with $\beta$-blocker use and CV anomalies noted among studies that did not exclude/adjust for diabetes mellitus (OR=0.85; 95% CI, 0.18–4.18; Figure 3A). Studies with potential for recall bias showed significant association with CV anomalies (OR=2.60; 95% CI, 1.24–5.47), whereas studies that used prospectively collected data showed no association (OR=1.67; 95% CI, 0.75–3.71; Figure S3). To further explore this heterogeneity, we stratified studies according to indication of $\beta$-blocker use. Studies where hypertension was the main indication showed statistical significance (OR=2.36; 95% CI, 1.67–3.34), compared with unspecified indications (OR=0.28; 95% CI, 0.03–2.25), with reduced heterogeneity in subgroups (Figure S4).

The results for CL/P (OR=3.11; 95% CI, 1.79–5.43; 2 studies) and for NT defects (OR=3.56; 95% CI, 1.19–10.67; 2 studies) were also statistically significant (Figure 3B and 3C). There was no evidence of heterogeneity or publication bias. The association of $\beta$-blockers with severe hypospadias (OR=2.27; 95% CI, 0.69–7.46) was statistically nonsignificant based on a single study.$^{13}$ No subgroup analyses could be performed for these outcomes because of very few studies.

### Sensitivity Analyses

After removing 2 studies at a time for the CL/P analysis, retaining only either Puhó et al$^8$ (b) or Puhó et al$^8$ (c) data sets with Davis et al,$^20$ the results were still statistically significant. However, when analyzing only the Puhó et al$^8$ (a) data set with Davis et al,$^20$ the results became statistically nonsignificant. This indicates that 2 of 3 data sets were influential, and that the results largely remained significant even after accounting for double counting of controls. However, for NT defects, removal of the Medveczky et al$^9$ (a) data set made the results nonsignificant, although removing the Medveczky et al$^9$ (b) data resulted in retained significance. This analysis is susceptible to the multiple comparison issue, and findings are less robust than that of CL/P.

### Discussion

The rate of antihypertensive use in pregnancy is rapidly escalating. $\beta$-blockers are the most common antihypertensive used during the first trimester, with ≈1 in 200 pregnant women exposed to these agents.$^1,^2$ Our systematic search found 13 case–control and cohort studies that examine this issue. Our meta-analyses incorporating 12 of these studies showed that use of $\beta$-blockers during the first trimester of pregnancy was associated with increased odds of CV anomalies, CL/P, and NT defects, although the primary outcome of all or major congenital anomalies was nonsignificant.

There are a few explanations for our findings of positive organ-specific associations without an overall increase in odds of all anomalies. The first is that these organ-specific effects are real and get diluted when we pool other anomalies that are not increased. This seems unlikely to fully account for our findings given that these organ-specific anomalies form a significant proportion of all anomalies. An alternative explanation is publication bias for organ-specific anomalies. Although the formal publication bias statistical tests for this outcome were nonsignificant, these tests are severely underpowered given small numbers of studies. It is also notable that the studies included in the analysis of overall malformations and organ-specific anomalies are, with the exception of 2 studies,$^8,^{9,13,26}$ different. One of these 2 studies$^{20}$ did not show significant results for either overall or organ-specific anomalies. Additional potential explanations include differences in the populations studied, type and dose of $\beta$-blockers used, potential differential misclassification of exposure in retrospective case–control studies, or the accuracy with which malformations are detected.
Table. Characteristics of 12 Studies That Examine the Association Between β-Blocker Exposure and Congenital Malformations*  

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Country/Data Source</th>
<th>Specific β-Blocker</th>
<th>Period of Pregnancy of Drug Use</th>
<th>Indication of Drug Use</th>
<th>Class of Anomalies</th>
<th>Patients With DM Excluded/Adjusted†</th>
<th>Potential Recall Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banhidy 2011</td>
<td>CC (case-control) Hungary: HCAR, maternal information: prospective medical records, retrospective self-report</td>
<td>Metoprolol, oxprenolol, pindolol, propranolol</td>
<td>Included first trimester</td>
<td>Chronic HTN/other indications</td>
<td>All within 3 mo of live birth, excluding genetic or chromosomal aberrations</td>
<td>Not clear</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Caton 2009</td>
<td>CC (case-control) US: Population-based birth defects surveillance systems; maternal information: interview</td>
<td>Any</td>
<td>1 mo preconception through the third month of pregnancy</td>
<td>HTN</td>
<td>CV, excluding PDA, patent foramen ovale, or recognized single gene or chromosome abnormalities</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Caton 2008</td>
<td>CC (case-control) US: Population-based birth defects surveillance systems; maternal information: interview</td>
<td>Any</td>
<td>1 mo preconception through month 4 postconception</td>
<td>HTN</td>
<td>Severe hypospadias, excluding chromosome/gene abnormality or intersex condition</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cedergren 2002</td>
<td>CC (case-control) Sweden: Swedish Register Study, Child Cardiology Register, Medical Birth Register, medical records</td>
<td>Any</td>
<td>Not specified</td>
<td>Cardiac defects referred within 1 year of birth, excluding PDA and single umbilical artery</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medveczky 2004a</td>
<td>CC (case-control) Hungary: HCAR; exposure data: retrospective mailed questionnaire, prenatal log/nurse visits</td>
<td>Oxprenolol</td>
<td>Second month</td>
<td>Not specified</td>
<td>Nonsyndromic NT defects within 3 mo of birth or pregnancy termination</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Medveczky 2004b</td>
<td>CC (case-control) Hungary: HCAR; exposure data: retrospective mailed questionnaire, prenatal log/nurse visits</td>
<td>Pindolol</td>
<td>Second month</td>
<td>Not specified</td>
<td>Nonsyndromic NT defects within 3 mo of birth or pregnancy termination</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Nakhai-Pour 2010</td>
<td>CC (case-control) Canada: Quebec Pregnancy Registry</td>
<td>Selective and nonselective</td>
<td>First trimester</td>
<td>HTN</td>
<td>Major congenital malformations within first year of life</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Puhó 2006a</td>
<td>CC (case-control) Hungary: HCAR, maternal information: prospective medical records and retrospective self-report</td>
<td>Metoprolol</td>
<td>Third to fourth months‡</td>
<td>HTN</td>
<td>Posterior cleft palate within 3 mo of birth or pregnancy termination</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Puhó 2006b</td>
<td>CC (case-control) Hungary: HCAR, maternal information: prospective medical records and retrospective self-report</td>
<td>Oxprenolol</td>
<td>Third to fourth months‡</td>
<td>HTN</td>
<td>Posterior cleft palate within 3 mo of birth or pregnancy termination</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Puhó 2006c</td>
<td>CC (case-control) Hungary: HCAR, maternal information: prospective medical records and retrospective self-report</td>
<td>Oxprenolol</td>
<td>Second to third months</td>
<td>HTN</td>
<td>Cleft lip and palate 3 mo of birth or pregnancy termination</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Quiesser-Luft 1996</td>
<td>CC (case-control) Germany: Mainz birth defect monitoring system, maternal &amp; infant medical records</td>
<td>Any</td>
<td>First 3 months</td>
<td>Not specified</td>
<td>At least 1 major malformation within first week of life, excluding spontaneous abortions</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Davis 2011</td>
<td>RC (retrospective cohort) US: HMO Research Network records</td>
<td>Any</td>
<td>First trimester</td>
<td>HTN</td>
<td>All congenital anomalies within first year of life</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Erici 2009</td>
<td>PC (prospective cohort) Serbia: Maternal questionnaire, neonatal or fetal physical or pathological examination</td>
<td>Propranolol and metoprolol</td>
<td>First trimester</td>
<td>CV disorders</td>
<td>Minor or major anomalies at birth</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kallen 2003</td>
<td>RC (case-control) Sweden: Swedish Medical Birth Register, Congenital Malformation Register, Hospital Discharge Register</td>
<td>Any</td>
<td>First trimester</td>
<td>Not specified</td>
<td>CV (except PDA and single umbilical artery)</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Lennestål 2009</td>
<td>RC (case-control) Sweden: Swedish Medical Birth Register, Congenital Malformation Register, Hospital Discharge Register</td>
<td>Any</td>
<td>Early pregnancy</td>
<td>HTN</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*CC indicates case–control; CV, cardiovascular; DM, diabetes mellitus; HCAR, Hungarian Congenital Abnormality Registry; HTN, hypertension; NT, neural tube; PC, prospective cohort; PDA, patent ductus arteriosus; and RC, retrospective cohort.
†Whether diabetes mellitus was excluded/adjusted in any analyses in the article. For specific information on β-blocker use analyses, see Table S1.
‡Third to fourth mo of pregnancy included because of timing of fetal palate formation.
§This study is not included in the meta-analysis; more recent study by Lennestål et al25 with extended follow-up using the same data set is included.
Irrespective of the cause, the findings of strong associations with particular malformations provide a powerful incentive to perform more research in this area.

The subgroup analyses for CV defects highlight some of the factors that may explain heterogeneity and potential sources of bias. The studies that adjusted/excluded for diabetes mellitus remained significant (after upward bias of diabetes mellitus positive confounding taken into account), whereas the subgroup with no adjustment/exclusion of diabetes mellitus was nonsignificant. It is difficult to explain these nonsignificant findings given the known association between diabetes mellitus and malformations; chance may play some role in the patterns we observe here. In other subgroup analyses, there were statistically significant results for studies with potential recall bias compared with nonsignificant results for studies that did not have a possibility of this bias. This might be attributable to an element of differential misclassification, shifting the point estimate away from null in retrospective studies.

A Congenital cardiovascular defects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log(Odds Ratio)</td>
</tr>
<tr>
<td>Carlsen 2009</td>
<td>1.12</td>
</tr>
<tr>
<td>Lerenstiel 2009</td>
<td>0.98</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.98</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.02, Chi^2 = 1, df = 1 (P = 0.61), P = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.15 (P &lt; 0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

B Cleft lip/palate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log(Odds Ratio)</td>
</tr>
<tr>
<td>Davis 2011</td>
<td>1.04</td>
</tr>
<tr>
<td>Puho 2007a</td>
<td>1.07</td>
</tr>
<tr>
<td>Puho 2007b</td>
<td>1.03</td>
</tr>
<tr>
<td>Puho 2007c</td>
<td>1.01</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.01</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00, Chi^2 = 0, df = 1 (P = 0.61), P = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.15 (P &lt; 0.0001)</td>
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C Neural tube defects

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>log(Odds Ratio)</td>
</tr>
<tr>
<td>Davis 2011</td>
<td>1.04</td>
</tr>
<tr>
<td>Medveczky 2004a</td>
<td>1.03</td>
</tr>
<tr>
<td>Medveczky 2004b</td>
<td>1.03</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<tr>
<td>Heterogeneity: Tau^2 = 0.00, Chi^2 = 0, df = 1 (P = 0.61), P = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.15 (P &lt; 0.0001)</td>
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</table>
However, we do not actually know whether there truly was recall bias, just that there was a possibility; it could also be nondifferential misclassification in prospective studies attenuating the results toward null. The CV studies that had hypertension as indication showed significant results compared with nonsignificant result of study where indication was not specified. However, we assume that even when indication was unspecified, the majority of subjects would still actually be using these drugs for hypertension; therefore, this analysis is likely somewhat artificial. Furthermore, absence of statistical significance in any of these analyses could also be attributable to lack of power.

To the best of our knowledge, this is the first meta-analysis in the literature examining the association of oral β-blocker usage in the first trimester of pregnancy on congenital anomalies. The strengths of this analysis include a comprehensive search strategy designed to identify all pertinent data on this subject, careful extraction of study data by multiple authors, and rigorous statistical methodology. An additional strength is our careful attention to the potential confounding role of diabetes mellitus. This is important given the known association of poorly controlled maternal diabetes mellitus and congenital anomalies in offspring and the coexistence of chronic hypertension and diabetes mellitus as part of the metabolic syndrome. Furthermore, the studies on which we based these analyses were generally population based with large sample sizes.

This review, however, does have some limitations. Six included studies were potentially subject to recall bias, in which exposure information and prenatal medication usage was collected through maternal interviews after delivery. Because the outcome had already occurred, mothers of infants with congenital malformations may be more likely to recall the exposure (the use of β-blockers), thus introducing potential recall bias and differential misclassification. Recording bias would have the same effect. Retrospective interview-based studies tended to find associations, whereas prospective prescription-based data did not, which can also be because women in the prescription database stopped using their prescriptions, leading to nondifferential misclassification and attenuating the estimate toward the null. Most studies did not include miscarriages, thus introducing an element of survivor bias that may affect generalizability of the results.

In addition, most studies do not clearly report the indication for β-blocker use. Hypertension, which is the leading indication for β-blockers, may itself be associated with congenital malformations and act as a confounder. None of the studies compared the risk of malformations in β-blockers with alternative treatments for hypertension, such as methyldopa, calcium channel blockers, or diuretics; this is an important limitation to the available literature and an important focus for future research. There is a small significant increased risk shown in some studies of hypertension itself (41% for CV defects and 43% for NT defects), but our estimates are much stronger than these reported estimates, which may indicate risk over and above that of underlying hypertension. Women taking β-blockers may be taking concurrent medications, but this information was not available from the included studies.

The studies had variability in timing of exposure within the first trimester (Table). Also, it was not reported whether the exposure was continued in subsequent trimesters. There were little to no data describing dosages or frequency of β-blocker use, and many articles did not report which specific β-blockers were used. The small number of studies in each category precluded subgroup analyses according to β-blocker type. It is also noteworthy that the significant CL/P and NT defect results were primarily driven by the use of oxprenolol. This nonselective lipophilic β-blocker is no longer frequently used, and it should be noted that all articles documenting its use were from Hungary, with data before 1997. Therefore, the inclusion of this drug may limit applicability of the findings. It is not known whether it had differential association with CL/P and NT defects compared to other β-blockers, particularly lipophilic ones, such as metoprolol, pindolol, propranolol, or labetalol; although there is no evidence that its mechanism of action is different from other β-blockers. Finally, all studies were performed in developed countries with largely white populations. However, there is no reason to postulate that racially/ethnically dissimilar populations would have different teratogenic responses to β-blockers.

Our meta-analysis suggests an increased risk of CV, oral, and NT defects with oral β-blocker exposure during the first trimester of pregnancy. The strength and causality of this association is difficult to ascertain because of the limited number of published studies, heterogeneity between studies, and potential biases, particularly confounding by indication and publication bias. In the future, more accurate and complete data should be collected about β-blocker use, timing of exposure, and confounders to further study this, preferably in the setting of large-scale observational studies, if possible. Future studies should also compare β-blockers with other antihypertensives, and to dissociate the effect of underlying hypertension from β-blocker use, by incorporating untreated hypertensive controls as a comparison group.

**Perspectives**

In conclusion, our meta-analysis of available data showed no increase in overall congenital malformations associated with first-trimester exposure to β-blockers. However, in organ-specific analyses, a 2-fold increase in the risk of CV defects and >3-fold increase in oral clefts and NT defects were found. These organ-specific findings may either be true associations given their magnitude or be attributable to publication bias or potential differential misclassification of exposure, for which further research is warranted given the frequency of exposure to these medications in early pregnancy. The current literature assessing risk is limited by lack of comparisons with alternative antihypertensives and untreated hypertension, and future research should address this deficit. Given the increasing incidence of hypertension, more information is needed to ensure that healthcare providers treat hypertensive pregnant women, as well as those with the potential to become pregnant, with the least teratogenic antihypertensive available.

**Acknowledgments**

All authors made substantial contributions to article design, analysis, and interpretation of data, and drafting and revising the article. All approve of the final version to be published.
Disclosures

IRB approval/informed consent is not applicable as this article involves a meta-analysis only of previously published articles involving de-identified data. This was an unfunded study. Sonia Hernandez-Diaz is the Principal Investigator (PI) of NIH R01 HD046595-01A on teratogenicity of drugs commonly used in pregnancy and NIH R01 HD059861-01A grant on phthalates in medications and risk of male genital malformations. She receives sponsorships from Agency of Healthcare Research and Quality (Grant RO1 HS018533) on antidegenerative drug treatment of pregnant women and congenital abnormalities in their offspring: a population-based study.

The other authors report no conflicts.

References


Novelty and Significance

What Is New?

- Data about teratogenic risks of first trimester use of oral β-blockers have not been summarized previously.

What Is Relevant?

- In organ-specific meta-analyses, increased odds of cardiovascular defects, cleft lip/palate, and neural tube defects were observed.

Summary

This meta-analysis suggests β-blockers may be associated with organ-specific teratogenicity. Given the increasing incidence of hypertension, more information is needed to ensure that healthcare providers use the least teratogenic antihypertensives available.
Online Supplemental Material

The Risk Of Congenital Malformations Associated With Exposure To Beta-Blockers Early In Pregnancy: A Meta-Analysis

Authors: Mohammad Y Yakoob MD MS¹, Brian T Bateman MD MSc², Eugenia Ho MD³, Sonia Hernandez-Diaz MD MPH DrPH⁴, Jessica M Franklin PhD⁵, Julie E Goodman PhD DABT⁶, Rebecca A Hoban MD MPH⁷

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6: Principal, Gradient Corp, 20 University Road, Cambridge, MA 02138, USA.

7: Assistant Professor of Pediatrics, Section of Neonatology, Rush University Medical Center, 1653 W. Congress Pkwy, 622 Murdock Building, Chicago, IL 60612, USA.
Power calculations: The methodology used is described by Cafri 2009\textsuperscript{1}. The macro used is below.

SAS code for power calculations:

```sas
%include 'P:\BIO 234\Meta-analysis Dec. 20, 2011\Cafri-BRM-2009\Cafri-BRM-2009\CafriFinal_macro.sas'; (This macro was obtained from the Supplementary Material in Cafri 2009).

data hedges13;
  input es v;
cards;
  0.015 0.003136
  -0.035 0.011236
  -0.174 2.099601
  -0.009 0.358801
  -0.105 0.3249
;
** POWER CALCULATION FOR META-ANALYSIS OF ANY ANOMALIES USING FIVE STUDIES **;
** POWER FOR OVERALL OR ANY CONGENITAL ANOMALIES **;
%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99, heterogeneity=99, n1=99, n2=99, k=99, eff_type='or', T=0.09531018, Dataset=hedges13, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99, heterogeneity=99, n1=99, n2=99, k=99, eff_type='or', T=0.182321557, Dataset=hedges13, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99, heterogeneity=99, n1=99, n2=99, k=99, eff_type='or', T=0.262364264, Dataset=hedges13, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

** POWER FOR CARDIOVASCULAR CONGENITAL ANOMALIES **;

data cv;
  input es v;
cards;
  0.956 0.143641
  1.015 0.0441
  -1.289 1.149184
  0.418 0.117649
;
%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99, heterogeneity=99, n1=99, n2=99, k=99, eff_type='or', T=0.693147181, Dataset=cv, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;
```
** POWER FOR CLEFT/LIP PALATE CONGENITAL ANOMALIES **;

```sas
%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=0.741937345, Dataset=cv, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=0.78845736, Dataset=cv, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;
```

** POWER FOR NEURAL TUBE DEFECTS CONGENITAL ANOMALIES **;

```sas
data clp;
input es v;
cards;
0.341 2.0164
0.742 0.251001
1.281 0.363609
1.435 0.190969
;
%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=1.131402111, Dataset=clp, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=1.16315081, Dataset=clp, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=1.193922468, Dataset=clp, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;
```

```sas
%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=1.223775432, Dataset=ntd, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=1.252762969, Dataset=ntd, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;

%metapower (test='M', model='random', raw_data='yes', alpha=.05, tau2=99,
  heterogeneity=99, n1=99, n2=99, k=99, eff_type='or',
  T=1.28093845, Dataset=ntd, B=NA, v=v, x=NA, es=es, p=NA, weight=NA); run;
```
SUPPLEMENTAL REFERENCES

**SUPPLEMENTAL TABLE**

Table S1. Data on congenital malformations associated with beta-blocker use in individual studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases (exposed cases)</th>
<th>No. of controls (exposed controls)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI) (if available)</th>
<th>Factors adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banhidy 2011</td>
<td>22,843 (520)</td>
<td>38,151 (856)</td>
<td>Overall: 1.02 (0.91 – 1.13)*</td>
<td>Overall: 0.7 (0.6 – 0.9)†</td>
<td>Maternal age, birth order, marital and employment status, other maternal diseases and pregnancy supplements</td>
</tr>
<tr>
<td>Caton 2009</td>
<td>5,021 (31)</td>
<td>4,796 (10)</td>
<td>-</td>
<td>CV: 2.6 (1.2 – 5.3)</td>
<td>Study center, maternal age at delivery, pre-pregnancy body mass index (BMI), gestational diabetes</td>
</tr>
<tr>
<td>Caton 2008</td>
<td>758 (5)</td>
<td>2,058 (6)</td>
<td>Severe hypospadias: 2.27 (0.69 – 7.46)*</td>
<td>-</td>
<td>Study center, age, race/ethnicity, parity, plurality, pre-pregnancy BMI, preexisting DM and gestational diabetes‡</td>
</tr>
<tr>
<td>Cedergren 2002</td>
<td>269 (1)</td>
<td>524 (7)</td>
<td>CV: 0.28 (0.01 – 2.17)</td>
<td>Same as unadjusted</td>
<td>Maternal age</td>
</tr>
<tr>
<td>Medveczky 2004a</td>
<td>1202 (1)</td>
<td>38,151 (23)</td>
<td>-</td>
<td>NT: 1.4 (0.2 – 10.0)</td>
<td>Maternal diseases</td>
</tr>
<tr>
<td>Medveczky 2004b</td>
<td>1202 (2)</td>
<td>38,151 (10)</td>
<td>-</td>
<td>NT: 5.8 (1.3 – 26.4)</td>
<td>Maternal diseases</td>
</tr>
<tr>
<td>Nakhai-Pour 2010</td>
<td>4,155 (3)</td>
<td>54,878 (40)</td>
<td>Overall: 0.99 (0.31 – 3.21)</td>
<td>-</td>
<td>Maternal age, education level, welfare, urban dweller, number of physicians visits/past year,</td>
</tr>
</tbody>
</table>
hospitalizations/emergency visits, number of prescribers during pregnancy, number of prenatal visits, CV diseases, DM, asthma, depression, chronic and gestational hypertension, antihypertensive medication use during different trimesters as appropriate‡

Puho 2006a

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of exposed cases</th>
<th>No. of unexposed cases</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Confounders adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puho 2006a</td>
<td>601 (4)</td>
<td>38,151 (120)</td>
<td>-</td>
<td>Posterior cleft palate (PCP): 2.1 (0.8 – 5.7)</td>
<td>Maternal age, parity</td>
</tr>
<tr>
<td>Puho 2006b</td>
<td>601 (3)</td>
<td>38,151 (50)</td>
<td>-</td>
<td>PCP: 3.6 (1.1 – 11.7)</td>
<td>Maternal age, parity</td>
</tr>
<tr>
<td>Puho 2006c</td>
<td>1,374 (6)</td>
<td>38,151 (41)</td>
<td>-</td>
<td>Cleft lip and palate: 4.2 (1.8 – 10.0)</td>
<td>Maternal age, employment status, parity, acute maternal diseases in 2nd or 3rd months of pregnancy</td>
</tr>
<tr>
<td>Quiesser-Luft 1996</td>
<td>1,472</td>
<td>9,682</td>
<td>Overall: 0.9 (0.3 – 2.8)*</td>
<td>-</td>
<td>None</td>
</tr>
</tbody>
</table>

Cohort studies

Davis 2011

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of exposed cases</th>
<th>No. of unexposed cases</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>Confounders adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis 2011</td>
<td>188 (25)</td>
<td>49,648 (6806)</td>
<td>CV: 1.52 (0.78 – 2.98) CL/P: 1.41 (0.09 – 22.74) NT: 4.46 (0.27 – 73.32)</td>
<td>Overall: 0.97 (0.78 – 1.19)$</td>
<td>Health system, maternal age, birth season</td>
</tr>
<tr>
<td>Study</td>
<td>Cases</td>
<td>Controls</td>
<td>OR (95% CI)</td>
<td>CV (95% CI)</td>
<td>Confounders</td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
<td>----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Eric 2009&lt;sup&gt;13&lt;/sup&gt;</td>
<td>10 (0)</td>
<td>6089 (326)</td>
<td>Overall: 0.84 (0.05 – 14.38)</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>Kallen 2003&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
<td>1548 (25)</td>
<td>-</td>
<td>CV: 1.85 (1.24 – 2.75)</td>
<td>Year of birth, maternal age, parity, smoking in early pregnancy, period of involuntary childlessness</td>
</tr>
<tr>
<td>Lennestal 2009&lt;sup&gt;15&lt;/sup&gt;</td>
<td>798 (25)</td>
<td>1,046,843 (12,660)</td>
<td>CV: 2.76 (1.79 – 4.08)</td>
<td>Year of birth, maternal age, parity, smoking, BMI (Diabetics excluded)</td>
<td></td>
</tr>
</tbody>
</table>

* Unadjusted estimates used for these studies because adjusted estimates not provided. Ritodrine information was excluded.
† Comparison of cases vs. controls in women with chronic hypertension (CH). Overall adjusted OR combining women with and without CH not presented.
‡ Beta-blocker use OR not provided with adjustment for confounders. These confounders adjusted for in other analyses.
§ RR estimate given (RR = 0.97; 95% CI: 0.81 – 1.16) converted into odds ratio for analysis.<sup>16</sup>
|| Study not included in meta-analysis; more recent study by Lennestal et al. with extended follow-up using same dataset is included.
SUPPLEMENTAL FIGURES

Figure S1. Forest plot for studies analyzing all or major anomalies stratified by potential recall bias.
Figure S2. Forest plot for studies analyzing all or major anomalies stratified by indication for beta-blocker use.
Figure S3. Forest plot for studies analyzing cardiovascular defects stratified by potential recall bias.

<table>
<thead>
<tr>
<th>Study</th>
<th>Log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caton 2009</td>
<td>0.96</td>
<td>0.38</td>
<td>25.9%</td>
<td>2.60 [1.24, 5.47]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>25.9%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 2.52 (P = 0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.6.4 No recall bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cedergren 2002</td>
<td>-1.29</td>
<td>1.07</td>
<td>5.7%</td>
<td>0.28 [0.03, 2.25]</td>
</tr>
<tr>
<td>Davis 2011</td>
<td>0.418</td>
<td>0.34</td>
<td>28.5%</td>
<td>1.52 [0.78, 2.99]</td>
</tr>
<tr>
<td>Lennestal 2009</td>
<td>1.015</td>
<td>0.22</td>
<td>39.8%</td>
<td>2.76 [1.83, 4.16]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>74.1%</td>
<td>1.67 [0.75, 3.71]</td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.30; Chi² = 6.03, df = 2 (P = 0.05); I² = 67%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall</td>
<td>Z = 1.26 (P = 0.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>100.0%</th>
<th>2.01 [1.18, 3.42]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity:</td>
<td>Tau² = 0.14; Chi² = 6.23, df = 3 (P = 0.10); I² = 52%</td>
<td></td>
</tr>
<tr>
<td>Test for overall efficiency:</td>
<td>Z = 2.56 (P = 0.01)</td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences:</td>
<td>Chi² = 3.64, df = 1 (P = 0.43), I² = 0%</td>
<td></td>
</tr>
</tbody>
</table>
Figure S4. Forest plot for studies analyzing cardiovascular defects stratified by beta-blocker use indication.